CLAIMS

1. A method of diagnosing non-small cell lung cancer (NSCLC) or a predisposition to developing non-small cell lung cancer in a subject, comprising determining the expression level of a non-small cell lung cancer-associated gene in a biological sample derived from the subject, wherein an increase of said expression level compared to a normal control level of said gene indicates that said subject suffers from or is at risk of developing NSCLC, wherein said NSCLC-associated gene is selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

2. The method of claim 1, wherein said increase is at least 10% greater than said normal control level.

3. The method of claim 1, wherein said method further comprises determining the expression level of a plurality of NSCLC-associated genes.

4. The method of claim 1, wherein said expression level is determined by any one method select from the group consisting of:
(1) detecting mRNA of the NSCLC-associated gene;
(2) detecting protein encoded by the NSCLC-associated gene; and
(3) detecting the biological activity of protein encoded by the NSCLC-associated gene.

5. The method of claim 1, wherein said expression level is determined by detecting hybridization of an NSCLC-associated gene probe to a gene transcript of said patient-derived biological sample.

6. The method of claim 5, wherein said hybridization step is carried out on a DNA array.

7. The method of claim 1, wherein said biological sample comprises sputum or blood.

8. A NSCLC reference expression profile, comprising a gene expression pattern of two or more genes selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

9. A kit comprising two or more detection reagents which detect the expression of one or more genes selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

10. An array comprising two or more polynucleotides which bind to one or more genes selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

11. A method of identifying a compound that inhibits the expression level of an NSCLC-associated gene, comprising the steps of:

(1) contacting a test cell expressing said NSCLC-associated gene with a test compound;
(2) detecting the expression level of said NSCLC-associated gene; and
(3) determining the compound that suppresses said expression level compared to a normal control level of said gene as an inhibitor of said NSCLC-associated gene
wherein said NSCLC-associated gene is selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

12. The method of claim 11, wherein said test cell is NSCLC cell.

13. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:
(1) contacting a test compound with a polypeptide selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1;
(2) detecting the binding activity between the polypeptide and the test compound; and
(3) selecting a compound that binds to the polypeptide.

14. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:
(a) contacting a test compound with a polypeptide encoded by a polynucleotide selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1;
(b) detecting the biological activity of the polypeptide of step (a); and
(c) selecting a compound that suppresses the biological activity of the polypeptide selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1 in comparison with the biological activity detected in the absence of the test compound.

15. The method of claim 14, wherein said biological activity is cell proliferative activity.

16. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:
(1) contacting a test compound with a cell expressing one or more marker genes, wherein the one or more marker genes is selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1; and
(2) selecting a compound that reduces the expression level of one or more marker genes selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

17. The method of claim 16, wherein said cell is NSCLC cell.

18. A method of screening for compound for treating or preventing NSCLC, said method comprising the steps of:

(1) contacting a test compound with a cell into which a vector comprising the transcriptional regulatory region of one or more marker genes and a reporter gene that is expressed under the control of the transcriptional regulatory region has been introduced, wherein the one or more marker genes are selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1;

(2) measuring the activity of said reporter gene; and

(3) selecting a compound that reduces the expression level of said reporter gene, as compared to a control.

19. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:

(1) contacting a KIF11 polypeptide or functional equivalent thereof with KOC1 polypeptide or functional equivalent thereof in the presence of a test compound;

(2) detecting the binding between the polypeptides; and

(3) selecting the test compound that inhibits the binding between the polypeptides.

20. The method of claim 19, wherein the functional equivalent of KIF11 polypeptide comprises amino acid sequence of KOC1 binding domain.

21. The method of claim 19, wherein the functional equivalent of KOC1 polypeptide comprises amino acid sequence of KIF11 binding domain.

22. A method of measuring RNA transporting activity of a polypeptide, said method comprising the steps of:

a. contacting a polypeptide selected from the group consisting of:

i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)*;

ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 2; and

iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

with a RNA to be transported and under the condition capable of RNA transporter formation;

b. detecting the level of the transported RNA; and

c. measuring the RNA transporting activity by correlating the level of the transported RNA of step (b) with the RNA transporting activity.

23. The method of claim 22, wherein the condition capable of RNA transporter formation is provided in the existence of KOC1 polypeptide or functional equivalent thereof.

24. The method of claim 23, wherein the functional equivalent of KOC1 polypeptide is a polypeptide selected from the group consisting of:

i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 104 *(KOC1)*;

ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 105 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 105;

iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 105; and

iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 104, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 105;

25. A method identifying an agent that modulate RNA transporting activity, said method comprising the steps of:

a. contacting the agent with a polypeptide selected from the group consisting of:

i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)*;

ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 2; and

iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

with a RNA to be transported and under the condition capable of RNA transporter formation;

b. detecting the level of the transported RNA; and

c. comparing the level of the transported RNA to a control level in the absence of the agent wherein an increase or decrease in the level of the transported RNA compared to control level indicates that the test compound modulates RNA transporting activity.

26. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:

(1) contacting a KOC1 polypeptide, or functional equivalent thereof with a RNA in the presence of a test compound;

(2) detecting the binding between the polypeptide and RNA; and

(3) selecting the test compound that inhibits the binding between the polypeptide and RNA.

27. The method of claim 26, wherein the functional equivalent of KOC1 polypeptide comprises amino acid sequence of either or both of RRM domain or KH domain.

28. A method of screening for a compound for treating or preventing NSCLC, said method comprising the steps of:

(1) contacting a GHSR1b or NTSR1 polypeptide, or functional equivalent thereof with NMU in the existence of a test compound;

(2) detecting the binding between the polypeptide and NMU; and

(3) selecting the test compound that inhibits the binding between the polypeptide and NMU.

29. The method of claim 28, wherein the polypeptide is expressed on the surface of a living cell.

30. The method of claim 29, wherein the binding between the polypeptide and NMU is detected by any one method select from the group consisting of:

(1) detecting the concentration of calcium or cAMP in the cell;

(2) detecting the activation of the polypeptide;

(3) detecting the interaction between the polypeptide and G-protein;

(4) detecting the activation of phospholipase C or its down stream pathway;

(5) detecting the activation of protein kinase cascade leading to activation of several kinases including Raf, MEK, ERKs, and protein kinase D (PKD);

(6) detecting the activation of a member of Src/Tec/Bmx-family of tyrosine kinases;

(7) detecting the activation of a member of the Ras and Rho family, regulation of a member of the JNK members of MAP families, or the reorganization of the actin cytoskeleton;

(8) detecting the activation of any signal complex mediated by the polypeptide activation;

(9) detecting the change in subcellular localization of the polypeptide including the

ligand-induced internalization/endocytosis of the polypeptide;

(10) detecting the activation of any transcription factor downstream of the polypeptides or the activation of their downstream gene; and

(11) detecting cell proliferation, transformation, or any other oncogenic phenotype.

31. A kit for detecting for an activity of a test compound to regulate RNA transporting activity, said kit comprising an isolated cell expressing the components of a to d, and culture medium supporting the cell growth.

a. a polypeptide selected from the group consisting of:

i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)*;

ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 2; and

iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 2;

b. a polypeptide selected from the group consisting of:

i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 104 *(KOC1)*;

ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 105 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 105;

iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 105; and

iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 104, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 105; and

c. a RNA to be transported; and

d. DCTN1

32. A kit for screening for a compound for treating or preventing NSCLC, said kit comprising at least following elements.

a. a polypeptide selected from the group consisting of:
   i. a polypeptide comprising the amino acid sequence of SEQ ID NO: 105 *(KOC1)*;
   ii. a polypeptide comprising the amino acid sequence of SEQ ID NO: 105 wherein one or more amino acids are substituted, deleted, or inserted, and said polypeptide has a biological activity equivalent to the polypeptide consisting of the amino acid sequence of SEQ ID NO: 105;
   iii. a polypeptide that comprises the amino acid sequence having at least about 80% homology to SEQ ID NO: 105; and
   iv. a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions to a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 104, wherein the polypeptide has a biological activity equivalent to a polypeptide consisting of the amino acid sequence of SEQ ID NO: 105;
   v. a polypeptide that comprises at least two KH domains and one or more RRM domain of SEQ ID NO:105; and
b. a RNA binding with said polypeptide.

33. The kit of claim 32, wherein the RNA is mRNA of gene selected from group consisting of genes listed in table 2.

34. A kit for screening for a compound for treating or preventing NSCLC, said kit comprising the components of:
a: GHSR1b or NTSR1 polypeptide, or functional equivalent thereof
b: NMU
c: reagent for detecting the binding between the polypeptide and NMU

35. A method of treating or preventing NSCLC in a subject comprising administering to said subject an antisense composition, said composition comprising a nucleotide sequence complementary to a coding sequence of a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

36. A method of treating or preventing NSCLC in a subject comprising administering to said subject an siRNA composition comprising an siRNA, wherein said composition reduces the expression of a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

37. The method of claim 36, wherein the siRNA is a sense strand comprising the nucleotide sequence selected from the group of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108, as the target sequence.

38. The method of claim 37, wherein the siRNA has the general formula
5'-[A]-[B]-[A']-3'
wherein [A] is a ribonucleotide sequence corresponding to a sequence selected from the group consisting of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108; [B] is a ribonucleotide sequence consisting of 3 to 23 nucleotides; and [A'] is a ribonucleotide sequence complementary to [A].

39. A method for treating or preventing NSCLC in a subject comprising the step of administering to said subject a pharmaceutically effective amount of an antibody or fragment thereof that binds to a polypeptide encoded by a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

40. A method of treating or preventing NSCLC in a subject comprising administering to said subject a vaccine comprising a polypeptide encoded by a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1 or an immunologically active fragment of said polypeptide, or a polynucleotide encoding the polypeptide.

41. A method for treating or preventing NSCLC in a subject, said method comprising the step of administering a compound that is obtained by the method according to any one of claims 13 to 23, and 28 to 34, or the agent that is identified by the method according to claim 27.

42. A method for treating or preventing NSCLC in a subject, said method comprising the step of administering a KOC1 mutant having dominant negative effect, or a polynucleotide encoding the mutant.

43. The method of claim 42, wherein the KOC1 mutant comprises an amino acid sequence lacking at least one KH domain located C-terminal of KOC1.

44. A double-stranded molecule comprising a sense strand and an antisense strand, wherein the sense strand comprises a ribonucleotide sequence corresponding to a KIF11, GHSR1b, NTSR1 or FOXM1 target sequence, and wherein the antisense strand comprises a ribonucleotide sequence which is complementary to said sense strand, wherein said sense strand and said antisense strand hybridize to each other to form said double-stranded molecule, and wherein said double-stranded molecule, when introduced into a cell expressing a KIF11, GHSR1b, NTSR1 or FOXM1 gene, inhibits expression of said gene.

45. The double-stranded molecule of claim 44, wherein said KIF11, GHSR1b, NTSR1 or FOXM1 target sequence comprises at least about 10 contiguous nucleotides from the nucleotide sequences selected from the group of SEQ ID NOs: 1, 3, 5, and 106.

46. The double-stranded molecule of claim 45, wherein said KIF11, GHSR1b, NTSR1 or FOXM1 target sequence comprises from about 19 to about 25 contiguous nucleotides from the nucleotide sequences selected from the group of SEQ ID NOs: 1, 3, 5, and 106.

47. The double-stranded molecule of claim 46, wherein said KIF11, GHSR1b, NTSR1 or FOXM1 target sequence is selected from the group consisting of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108.

48. The double-stranded molecule of claim 44, wherein said double-stranded molecule is a single ribonucleotide transcript comprising the sense strand and the antisense strand linked via a single-stranded ribonucleotide sequence.

49. The double-stranded molecule of claim 44 wherein the double-stranded molecule is an oligonucleotide of less than about 100 nucleotides in length.

50. The double-stranded molecule of claim 49, wherein the double-stranded molecule is an oligonucleotide of less than about 75 nucleotides in length.

51. The double-stranded molecule of claim 50, wherein the double-stranded molecule is an oligonucleotide of less than about 50 nucleotides in length.

52. The double-stranded molecule of claim 51, wherein the double-stranded molecule is an oligonucleotide of less than about 25 nucleotides in length.

53. The double-stranded polynucleotide of claim 52, wherein the double stranded molecule is an oligonucleotide of between about 19 and about 25 nucleotides in length.

54. A vector encoding the double-stranded molecule of claim 44.

55. The vector of claim 54, wherein the vector encodes a transcript having a secondary structure and comprises the sense strand and the antisense strand.

56. The vector of claim 55, wherein the transcript further comprises a single-stranded ribonucleotide sequence linking said sense strand and said antisense strand.

57. A vector comprising a polynucleotide comprising a combination of a sense strand nucleic acid and an antisense strand nucleic acid, wherein said sense strand nucleic acid comprises nucleotide sequence selected from the group consisting of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108, and said antisense strand nucleic acid consists of a sequence complementary to the sense strand.

58. The vector of claim 57, wherein said polynucleotide has the general formula

5'-[A]-[B]-[A']-3'
wherein [A] is a nucleotide sequence selected from the group consisting of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108; [B] is a nucleotide sequence consisting of 3 to 23 nucleotides; and [A'] is a nucleotide sequence complementary to [A].

59. A composition for treating or preventing NSCLC, said composition comprising a pharmaceutically effective amount of an antisense polynucleotide against a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

60. A composition for treating or preventing NSCLC, said composition comprising a pharmaceutically effective amount of an siRNA against a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

61. The composition of claim 60, wherein the siRNA comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 32, 33, 34, 35, 36, 37, and 108, as the target sequence.

62. A composition for treating or preventing NSCLC, said composition comprising a pharmaceutically effective amount of an antibody or fragment thereof that binds to a polypeptide encoded by a gene selected from the group consisting of KIF11, GHSR1b, NTSR1, and FOXM1.

63. A composition for treating or preventing NSCLC, said composition comprising a pharmaceutically effective amount of the compound selected by the method of any one of claims 13 to 23, and 28 to 34, or the agent that is identified by the method according to claim 27 as an active ingredient, and a pharmaceutically acceptable carrier.

64. A composition for treating or preventing NSCLC, said composition comprising a pharmaceutically effective amount of the KOC1 mutant having dominant negative effect, or a polynucleotide encoding the mutant as an active ingredient, and a pharmaceutically acceptable carrier.

65. The composition of claim 64, wherein the KOC1 mutant comprises an amino acid sequence lacking at least one KH domain located C-terminal of KOC1.

66. A method of predicting a NSCLC prognosis, wherein the method comprises the steps of:
a. detecting expressing level of either or both of KIF11 and KOC1 in a specimen collected from a subject whose NSCLC prognosis is to be predicted, and
b. indicating a poor prognosis when an elevation of the expressing level of either or both of KIF11 and KOC1 is detected.

67. The method of claim 66, wherein the expression level is detected by any one of the method selected from the group consisting of:

(a) detecting the mRNA encoding the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105 *(KOC1)*,

(b) detecting the protein comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105*(KOC1)*, and

(c) detecting the biological activity of the protein comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105 *(KOC1)*.

68. A kit for predicting a NSCLC prognosis, wherein the kit comprising any one component select from the group consisting of:

(a) reagent for detecting the mRNA encoding the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105 *(KOC1)*,

(b) reagent for detecting the protein comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105*(KOC1)*, and

(c) reagent for detecting the biological activity of the protein comprising the amino acid sequence of SEQ ID NO: 2 *(KIF11)* or SEQ ID NO: 105 *(KOC1)*.